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Health and Environmental Effects Profile for Nitroanilines

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR NITROANILINES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
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16. ABSTRACT

The Health and Environmental Effects Profile for nitroanilines was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for nitroanilines.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for nitroanilines is 100.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

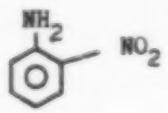
ADI	Acceptable daily intake
ATP	Adenosine triphosphate
BCF	Bioconcentration factor
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration levels)
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
ppm	Parts per million
RQ	Reportable quantity ranking
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

Nitroanilines are compounds derived by the substitution of aniline with one nitro group. Depending on the position of the nitro substituent, nitroaniline exists in three isomeric forms. This profile addresses the three isomers, o-, m- and p-nitroaniline.

1.1. STRUCTURE AND CAS NUMBER

1.1.1. **o-Nitroaniline.** This compound is also known as 1-amino-2-nitrobenzene, 2-nitroaniline, azoic diazo component 6, or 2-nitrobenzeneamine. The chemical structure, molecular formula, molecular weight and Chemical Abstract Services (CAS) registry number for this compound are given below:

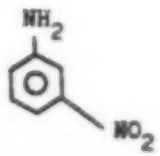


Molecular formula: $C_6H_6N_2O_2$

Molecular weight: 138.12

CAS Number: 84-74-4

1.1.2. **m-Nitroaniline.** This compound is also known as 1-amino-3-nitrobenzene, 3-nitroaniline, or 3-nitrobenzeneamine. The chemical structure, molecular formula, molecular weight and CAS registry number for this compound are as follows:



Molecular formula: $C_6H_6N_2O_2$

Molecular weight: 138.12

CAS Number: 99-09-2

1.1.3. p-Nitroaniline. The synonyms for p-nitroaniline are 1-amino-4-nitrobenzene, 4-nitroaniline, or 4-nitrobenzeamine. The chemical structure, molecular formula, molecular weight and CAS registry number for this compound are given below:

Molecular formula: $C_6H_6N_2O_2$

Molecular weight: 138.12

CAS Number: 100-01-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical properties of the three isomers of nitroaniline are given in Table 1-1.

Nitroanilines can be reduced chemically to aromatic diamines, as can other nitro-aromatics. The amine group in nitroanilines may undergo a number of chemical reactions including N-alkylation, acylation, oxidation, and diazotization. Some of these reactions, particularly diazotization, are used to manufacture dyes. The chemical reactions that are relevant to the environmental fate of the nitroanilines are discussed in Chapter 2.

1.3. PRODUCTION DATA

o-Nitroaniline is produced by high-pressure ammonolysis of o-chloronitrobenzene (Hall et al., 1980) or from nitration of acetanilide with subsequent removal of the acetyl group by hydrolysis (Hawley, 1977). m-Nitroaniline is produced by nitration of acetylated aniline with the subsequent removal of the acetyl group by hydrolysis (Hawley, 1977). This isomer can also be manufactured by the partial reduction of m-dinitrobenzene with sodium sulfide (Hall et al., 1980) or by nitration of aniline-borotrifluoride complex with mixed sulfuric-nitric acid at 0°C (Northcott, 1978).

TABLE 1-1

Selected Physical Properties of Nitroanilines*

Compound	o-Nitroaniline	m-Nitroaniline	p-Nitroaniline
Physical state	orange rhombic needles	yellow needles	yellow monoclinic needles
Melting point °C	71.5	111.8	147.5
Boiling point °C	284.1	305-307	331.7
Specific gravity	1.442_4^{20}	1.430_4^{20}	1.424_4^{20}
Vapor pressure	1 mm at 104°C	1 mm at 119.3°C	0.0015 mm at 20°C
Water solubility	1260 mg/ℓ at 25°C	890 mg/ℓ at 25°C	800 mg/ℓ at 19°C
Log octanol/water partition coefficient	1.69	1.37	1.39
pK_a	-0.22	2.46	1.0
Conversion factor	1 ppm = 5.74 mg/m³ at 20°C	1 ppm = 5.74 mg/m³ at 20°C	1 ppm = 5.74 mg/m³ at 20°C

*Source: Weast, 1980; Verschueren, 1983; Hansch and Leo, 1979; Morrison and Boyd, 1973

p-Nitroaniline may be manufactured by the ammonolysis of p-chloronitrobenzene or p-dinitrobenzene under pressure (Hall et al., 1980). Nitration of acetanilide followed by hydrolysis is another procedure for the production of p-nitroaniline (Hall et al., 1980).

According to the TSCA Production File, the following United States companies manufactured nitroanilines in 1977:

Company	Production Value Per Year (pounds)
o-Nitroaniline:	
Monsanto Co., Sauget, IL	1-10 million
GAF Corp., Rensselaer, NY	10,000-100,000
Blackman Uhler Chem. Div., Spartanburg, SC	10,000-100,000
E.I. DuPont Co., Deepwater, NJ	unknown
Crescent Chem. Co., Hauppauge, NJ	unknown

Company	Production Value Per Year (pounds)
p-Nitroaniline:	
Monsanto Co., Suget, IL	10-50 million
UOP Inc., Shreveport, LA	unknown
E.I. DuPont Co., Deepwater, NJ	unknown

The United States producers of nitroanilines in 1982 were as follows (USITC, 1983):

o-Nitroaniline:

E.I. DuPont Co., Deepwater, NJ

Monsanto Co., Sauget, IL

Company whose identification has been withheld

p-Nitroaniline:

American Color and Chem. Corp., Charlotte, NC

E.I. DuPont Co., Deepwater, NJ

Monsanto Co., Sauget, IL

The Directory of Chemical Producers (SRI, 1984) lists Monsanto Company as the only United States manufacturer of o-nitroaniline as of January, 1984. With the exclusion of American Color and Chemical Corp. and the inclusion of UOP, Inc., it includes the other two companies listed in USITC (1983) as the United States manufacturers of p-nitroaniline. Current domestic producer(s) and the production data for m-nitroaniline are not available. In 1981, the total United States production of o- and p-nitroaniline were 6.8 million pounds and 13.7 million pounds, respectively (USITC, 1982). Current United States production data for either the o- or the p-isomer are not available.

1.4. USE DATA

o-Nitroaniline is used in the manufacture of pharmaceutical products, dyestuff and dye intermediates, rubber chemicals, veterinary products and photo antifogging agents (Hall et al., 1980). m-Nitroaniline is used predominantly as a dye intermediate. It is also used to manufacture photographic antifogging agents, coccidostatics, interior paint pigments and artificial sweeteners (Hall et al., 1980). p-Nitroaniline is used in the manufacture of rubber chemicals, dyes and intermediates, gasoline additives, pharmaceuticals and veterinary products, agricultural chemicals and miscellaneous other uses, such as corrosion inhibition (Hall et al., 1980; Hawley, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. ATMOSPHERE

No comprehensive study on the fate and transport of nitroanilines in the atmosphere is available in the literature. Based on the chemical structure and fate of these compounds in aquatic media, it is possible to speculate about some of their possible reactions in the atmosphere. The amino group of the nitroanilines may be susceptible to oxidation. The likely processes that can oxidize these compounds in the atmosphere are interactions with hydroxy radicals and molecular oxygen and photochemical reactions. Since the quantitative data on the rate constants of these reactions are not available, it is not possible to predict either the atmospheric half-life or the primary process that may control the fate of these chemicals in the atmosphere.

The intramedia transport of nitroanilines should be related directly to their lifetimes in the atmosphere. Compounds with longer lifetimes will have a better chance to transport longer distances in the atmosphere. Considering the reasonably high aqueous solubility of these compounds, significant transport of these compounds from the atmosphere to surface water and soil through wet deposition seems likely.

2.2. WATER

Although information pertaining to the fate and transport of nitroanilines in aquatic media is more abundant than information regarding their fate and transport in air, it is still inadequate to make a comprehensive assessment of its aquatic fate. Chemically, these compounds could react with the available free radicals in the aquatic media and/or undergo direct photochemical reactions. No information on the reactivity of these compound

with RO_2 radicals, singlet oxygen ($^1O_2$) and other available free radicals is available. The o-, m- and p-nitroanilines have absorption maxima at 285, 280 and 380 nm, respectively, in aqueous solutions (Alexander and Lustigman, 1966). The p-isomer has an absorption band at wavelength >290 nm (Barltrop and Bunce, 1968; Howard et al., 1976). It is known that p-nitroaniline when irradiated with light of wavelength >290 nm forms $\cdot C_6H_4NO_2$ free radicals (Chignell et al., 1980). Similarly, it has been demonstrated by Barltrop and Bunce (1968) that photolysis of o-nitroaniline in a solvent with abstractable hydrogen atom at wavelength >290 nm produces aniline. In triethylamine solvent, 16% of the compound was degraded in 3 hours of irradiation. All of these results indicate that o- and p-nitroaniline, at least, may undergo some photoreaction in aquatic media, although the significance of this reaction in determining the overall fate cannot be ascertained.

The prolonged heating of o-nitroaniline with aqueous alkali has been reported to yield o-nitrophenol (Liang, 1963). Judging from the conditions under which this hydrolysis was observed, it is unlikely that any of the nitroanilines will undergo significant hydrolysis under natural aquatic conditions. Endyus'kin and Fidippov (1980) reported the oxidation of p-nitroaniline during 2 hours of chlorination of wastewater from dye manufacturing at 70°C and a pH of 9. This result raises the possibility of oxidation of any residual nitroaniline in drinking water during the chlorination step of the treatment process.

The nitrosation of both o- and p-nitroaniline by nitrogen oxides in neutral and/or alkaline solutions was reported by Challis et al. (1978). Although such reactions may have physiological significance, it is unlikely that nitrosation will be a significant fate-determining process in most natural aquatic systems.

The degradation of nitroanilines with both pure cultures and mixed cultures of microorganisms has been reported by several investigators. Microorganisms isolated from wastewater of a caprolactam production plant showed high activity for the degradation of p-nitroaniline (Stavskaya et al., 1975). The isolation of microorganisms capable of degrading p-nitroaniline from a biofilm and the activated sludge have been reported (Udod, 1973; Udod et al., 1972, 1974). The microorganisms belonged to the genera Pseudomonas and Bacillus and had the ability to degrade p-nitroaniline at concentrations up to 2000 mg/ℓ. The o-isomer was degraded (85-90%) at a concentration of 100 mg/ℓ. A decrease of redox potential of the media enhanced degradation of nitroanilines. The pathway from p-nitroaniline degradation was through formation of p-phenylenediamine and p-aminophenol intermediate products.

The utilization of amino and nitro groups of nitroanilines during the growth of freshwater algae, Chlorella valgaris, was reported by Villeret (1965). The degradation of the m-isomer was found to be faster than the p-isomer, with the o-isomer being the least degradable with this alga.

The biodegradability of nitroanilines by a mixed culture of organisms was reported by several investigators. With activated sludge as inoculum, all three isomers of nitroaniline were reported to be nonbiodegradable at a concentration of 100 mg/ℓ and an incubation time of 2 weeks (Kitano, 1978). Hallas and Alexander (1983) reported <15% decomposition of o-nitroaniline incubated with municipal sewage for 60 days under aerobic conditions and ~63% decomposition under anaerobic conditions. Faster degradation of nitroanilines was reported with microorganisms after a lag period of ~12-20 days, which evidently caused acclimatization of microorganisms (Young and Affleck, 1974; Kincannon and Esfandi, 1981). With acclimated sewage,

p-nitroaniline biodegraded only partially in an aerobic environment. The o-isomer was not biodegradable even with acclimated microorganisms (Young and Affleck, 1974). Similarly, a 59% removal of o-nitroaniline present at an initial concentration of 12.4 mg/ℓ was reported upon incubation of the wastewater for 2 days with acclimated activated sludge (Kincannon and Esfandi, 1981). Pitter (1976), however, observed no biodegradation of any of the three nitroanilines at concentrations of 25-30 mg/ℓ upon incubation with adapted activated sludge for 20 days.

This information suggests that the available studies concerning the biodegradability of nitroanilines are conflicting. It is not possible to assess the significance of biodegradation of these compounds in natural surface waters.

Data in the available literature concerning the transport of nitroanilines in aquatic media are inadequate. The predicted evaporation half-life of p-nitroaniline from aquatic media is ~106 days (U.S. EPA, 1982). Since the vapor pressure data for the other two isomers at ambient temperatures are not known, it is difficult to predict the evaporation half-lives of these isomers. Considering the higher aqueous solubilities and expected comparable vapor pressures, both the o- and the m-isomers are not likely to volatilize significantly from aqueous media.

No information on the transport of nitroaniline from the aquatic phase of water bodies, to the bottom sediment through adsorption and subsequent precipitation, is available. Based on the logarithm of soil sorption coefficients (K_{om}) for m- and p-nitroanilines of 1.49 and 1.64 (Briggs, 1981), it is likely that moderate removal through adsorption and subsequent precipitation will take place.

The overall persistence of the nitroanilines in river water in the Netherlands was studied by Zoeteman et al. (1980). The half-lives for o-, m- and p-nitroaniline were estimated at 2.3, 1.0 and 3.8 days, respectively.

There are no experimental values in the literature on the bioaccumulation of nitroanilines in aquatic species. Based on the calculated BCFs of 12, 8 and 6 for o-, m- and p-nitroaniline, respectively (Howard et al., 1976), it is unlikely that any of the nitroanilines will bioaccumulate significantly in aquatic species.

2.3. SOIL

No information concerning the photochemical or any other chemical reactivity (e.g., hydrolysis, free radical reactions) of nitroanilines in soil is available. The microbial degradation of nitroanilines by soil microorganisms has been reported by a few investigators. A strain of Pseudomonas isolated from soil used p-nitroaniline as a sole source of carbon (Zeyer and Kearney, 1983); however, o- and m-nitroaniline were not degradable by the same strain. A soil fungus, Geotrichum candidum, which biodegraded aniline and several substituted anilines, failed to biodegrade all three nitroanilines (Bordeleau and Bartha, 1972). When 10 mg/ℓ of o- and m-nitroaniline and 5 mg/ℓ of p-nitroaniline were incubated with a 1% suspension of a silt loam soil, these compounds persisted for >64 days (Alexander and Lustigman, 1966). It is, therefore, likely that biodegradation of the nitroanilines in soil will be a slow process.

Insufficient data pertaining to the transport of the nitroanilines in soil are available. Based on the logarithm of soil sorption data (log K_{om}) of 1.49 and 1.64 for m- and p-nitroaniline (Briggs, 1981), these two compounds should be moderately mobile in soil.

3. EXPOSURE

No monitoring data for any of the three nitroanilines are available in STORET. Games and Hites (1977) reported the detection of 0.27 mg/ℓ of unspecified nitroaniline in the raw wastewater from a United States dye manufacturing plant. No nitroaniline was detected in the treated effluent from the same wastewater. Meijers and Van Der Leer (1976) detected (not quantified) the presence of o-nitroaniline in the River Waal at Brakel in the Netherlands. Piet and Morra (1983) reported p-nitroaniline at a concentration of 0.001 mg/ℓ in the water of the River Rhine in the Netherlands. No p-nitroanline was detected, however, in the tap water obtained from this river water. All three isomers of nitroaniline, the o-, m- and p-nitroaniline, were detected at concentrations of 0.001, 0.0001 and 0.001 mg/ℓ, respectively, in water from the River Lobith in the Netherlands (Zoeteman et al., 1980). No monitoring data for any of these chemicals in air or foods were available in the literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

The recovery of ~85.7% of the administered radioactivity from the urine within 24 hours of dosing rats by gavage with 5 mg/kg bw of ^{14}C-p-nitroaniline indicated that ^{14}C-p-nitroaniline was readily absorbed from the gastrointestinal tract (Mate et al., 1967). ^{14}C-p-Nitroaniline was also readily absorbed from the peritoneal cavity as indicated by the recovery of ~80.9% of the administered radioactivity in the urine within 24 hours after i.p. injection of 5 mg/kg bw of ^{14}C-p-nitroaniline (Mate et al., 1967). p-Nitroaniline is rapidly absorbed through the skin (OSHA/NIOSH, 1978).

Pertinent data regarding the absorption of o- or m-nitroaniline were not located in the literature as cited in the Appendix.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of o-, m- or p-nitroaniline were not located in the literature as cited in the Appendix.

4.3. METABOLISM

Analysis of the acid-hydrolyzed urine from rats that had received, either by gavage or i.p. injection, 5 mg/kg bw of ^{14}C-p-nitroaniline indicated that the radioactive compounds appearing in the urine were p-nitroaniline, p-phenylenediamine and 2-amino-5-nitrophenol (Mate et al., 1967). Of the total urinary radioactivity, 2-amino-5-nitrophenol comprised 43.1$\pm$2.5%, p-phenylenediamine comprised 26.1$\pm$6.8% and p-nitroaniline comprised 14.1$\pm$2.0%. In urine that was not acid-hydrolyzed, p-nitroaniline comprised only ~2% of the recovered radioactivity. No p-aminophenol and no p-nitrophenyl hydroxylamine, even after B-glucuronidase, sulphatase and/or acid hydrolysis treatment of the urine sample, was detected (Mate et al., 1967).

Incubation of hepatic microsomes from male Sprague-Dawley rats (200-400 g) with p-nitroaniline at a pH of 7.4 at 37°C for 1 hour resulted in the formation of 2-amino-5-nitrophenol (Anderson et al., 1984), which was the most abundant metabolite identified by Mate et al. (1967) in the urine of rats treated with p-nitroaniline either orally or i.p. No evidence of N-hydroxylation was observed in the microsomal incubation mixtures. Anderson et al. (1984) reported that a 2,3-epoxide may be an intermediate in the metabolism of p-nitroaniline to 2-amino-5-nitrophenol.

4.4. EXCRETION

The urine and feces were collected from one group of 6 male rats that received an oral dose by gavage of 5 mg/kg bw of ^{14}C-p-nitroaniline and from another group of 6 male rats that received an i.p. injection of 5 mg/kg bw of ^{14}C-p-nitroaniline (Mate et al., 1967). After both routes of administration, the amount of radioactivity excreted in the feces within 48 hours of dosing was minor (0.4±0.2% and 0.6±0.3% of the administered dose for the i.p. and the oral route, respectively) and most of the radioactivity was recovered from the urine within the first 24 hours after dosing (76.5±1.4% and 83.0±1.7% of the administered dose for the i.p. and oral route, respectively) (Table 4-1). Although no experimental details were given, Mate et al. (1967) concluded that, like fecal excretion, biliary excretion of p-nitroaniline was very minor.

Five hours after 100 µmol/kg bw (~13.8 mg/kg bw) of p-, m- or p-nitroaniline was administered i.p. to groups of 5 male rats, unspecified diazo-positive metabolites of the nitroaniline isomers were identified in the urine by reacting them with a diazonium salt (Watanabe et al., 1976).

TABLE 4-1

Excretion of ^{14}C by Rats Dosed with [^{14}C]-p-Nitroaniline*

Route of Administration	Dose (mg/kg bw)	Percentage of Dose Excreted in Urine			Feces
		24 Hours	48 Hours	72 Hours	48 Hours
Intraperitoneal	5	76.5 ± 1.4	2.8 ± 1.4	1.6 ± 0.6	0.4 ± 0.2
Oral	5	83.0 ± 1.7	1.7 ± 0.4	1.0 ± 0.8	0.6 ± 0.3

*Source: Mate et al., 1967

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of o-, m- and p-nitroaniline were not located in the literature as cited in the Appendix. The National Toxicology administered to mice by gavage; however, no data are available at the present time.

5.2. MUTAGENICITY

Chiu et al. (1978) reported that o-, m- and p-nitroaniline at concentrations of 0.1, 1.0 and 10.0 µmol (probably per plate) did not induce reverse mutations in Salmonella typhimurium strain TA100 in the absence of metabolic activation. At the same concentations, o- and m-nitroaniline did not induce reverse mutations in S. typhimurium strain TA98. At the highest concentration (10.0 µmol), however, p-nitroaniline tripled the number of reverse mutations in S. typhimurium strain TA98. None of the mutagenicity testing reported in the Chiu et al. (1978) study was done in the presence of metabolic activation.

There was a significant increase in the number of S. typhimurium strain TA1538 mutants when they were incubated in the presence of 50 and 100 µg/plate of o-, m- and p-nitroaniline and rat liver microsomal preparations (Garner and Nutman, 1977). The three nitroanilines were not mutagenic in the absence of metabolic activation (Garner and Nutman, 1977).

Malca-Mor and Stark (1982) reported that the mutagenicity of p-nitroaniline was dependent upon the pH of the testing medium. At pH 8.0, p-nitroaniline induced increased numbers of mutations in S. typhimurium TA1538 in the presence of S-9, but not in the absence of metabolic activation. At a pH of 7.4, p-nitroaniline induced increased numbers of mutant

colonies in S. typhimurium strain TA1538 in the absence of metabolic activation, but not in the presence of S-9. Although units of concentration of p-nitroaniline were reported, the dimension of the units is not clearly reported in the paper.

Thompson et al. (1983) reported on the mutagenicity of the three isomers of nitroaniline in S. typhimurium (strains G46, TA1535, TA100, C3076, TA1537, D3052, TA1538 and TA98) and in Escherichia coli strains WP2 and WP2uvrA$^-$ using a gradient plate procedure. Although tests were conducted both with and without metabolic activation, only the results obtained in the presence of the rat liver S-9 fraction were reported. o-Nitroaniline was reported to be nonmutagenic. m-Nitroaniline was mutagenic to S. typhimurium strains TA1535, TA100, TA1538 and TA98 at concentrations ranging from 30-100 µg/mL of agar. p-Nitroaniline was mutagenic to S. typhimurium strains D3052, TA1538 and TA98 at concentrations ranging from 1-300 µg/mL of agar.

Shah and Andrews (1979) reported, in an abstract, that p-nitroaniline (one of the oxidative products of the hair-dye p-phenylenediamine) was mutagenic to S. typhimurium strains TA1538 and TA98 only after metabolic activation, but not in TA100.

In a report regarding vegetable desmutagenic factors (i.e., substances that are able to inactivate known chemical carcinogens), Inoue et al. (1981) reported without specifying any additional details that o-, m- and p-nitroaniline in the absence of metabolic activation were not mutagenic to strains TA98 or TA100 of S. typhimurium.

Four hours after injecting 100 mg/kg bw of o-nitroaniline i.p. into Swiss CD1 male mice, the number of single-strand DNA breaks was elevated in both liver and kidney, although the difference was reported to be not

statistically significant (Cesarone et al., 1982). Similarly, none of the nitroanilines caused unscheduled DNA synthesis in primary cultures of adult rat hepatocytes (Thompson et al., 1983) when tested up to 500 nmoles/mL.

Groups of five (CBA x BALB/c) F_1 male mice received daily i.p. doses of 25, 50, 100, 250 or 500 mg/kg bw/day of p-nitroaniline for 5 days (Topham, 1980). Five weeks after the last treatment, the mice were killed and the morphology of the sperm from the cauda epididymus was evaluated. Apparently, p-nitroaniline did not induce an increase in sperm-head abnormality.

The English abstract of a Russian experiment reported that p-nitroaniline at a concentration of 0.001-0.004 M for 2 hours caused morphological changes (presumably mutants) in Actinomyces sphaeroides spores (Romanova and Rapoport, 1971).

The National Toxicology Program has tested p-nitroaniline for mutagenic effects in several in vitro systems: the Ames test (five standard strains), cytogenetics and sister chromatid exchange tests in Chinese hamster ovary (CHO) cells and the sex-linked recessive lethal test in Drosophila. Only the Ames test data has been published (Haworth et al., 1983) but positive results have been observed in all but the Drosophila assay.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of the nitroanilines were not located in the literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of the nitroaniline were not located in the literature as cited in the Appendix.

5.5. CHRONIC TOXICITY

In a meeting abstract, Houser et al. (1983) reported that rats had been treated by gavage with 0, 3, 10 or 30 mg/kg bw/day of p-nitroaniline for 90 days. There were no differences between treated and control rats in body weight gain, food consumption or clinical chemistry parameters. Rats treated with p-nitroaniline had, however, a dose-related increase in the blood level of methemoglobin, as well as decreased hematocrit and hemoglobin levels and increased reticulocyte counts and mean corpuscular volumes. Microscopic changes in the spleen, including excessive extramedullary hemopoiesis, hemosiderosis, splenic congestion and vacuolization of the red pulp, were reported in rats treated with all levels of p-nitroaniline (Houser et al., 1983).

Chhabra et al. (1983) reported in a meeting abstract that groups of five 8-week-old B6C3F$_1$ mice/sex/dose were treated by gavage with 0, 10, 30, 100, 300 or 1000 mg p-nitroaniline/kg bw/day for 16 days. There were no effects at any dose level on body weight gains and food consumption, but all the mice receiving 1000 mg/kg bw/day of p-nitroaniline died during the experiment. At a dose of 300 mg/kg bw/day, mice had significantly lower red blood cell counts and hematocrit values, increased hemoglobin and methemoglobin values, increased numbers of reticulocytes and leukocytes and enlarged spleen with extramedullary hematopoiesis and hemosiderin-containing Kupffer cells. Evaluation of the pertinent parameters was not reported at any other dose level (Chhabra et al., 1983).

In an abstract, Nair et al. (1983) reported that groups of 10 male and 10 female Sprague-Dawley rats were exposed to concentrations of 0, 10, 30 and 90 mg/m^3 of p-nitroaniline in air for 6 hours/day, 5 days/week, for 4 weeks. A dose-related increase in blood methemoglobin levels, as well as a

decrease in the number of red blood cells, hematocrit and hemoglobin levels, were reported. Splenic changes induced by p-nitroaniline, which were observed at all dose levels, included increased absolute and relative weight, pronounced congestion, extramedullary hematopoiesis and hemosiderosis (Nair et al., 1983). It should be noted that the adverse effects on the oxygen transporting capacity of the blood are consistent with cases of human poisoning in which onset of cyanosis and dyspnea occurred several hours after exposure to p-nitroaniline (Anderson, 1946; Belknap, 1957).

The English abstract of a Russian study (Vasilenko et al., 1974a) indicated that exposure of rats to 5 mg/m³ of p-nitroaniline for 5 hours/day for 4 months caused a decrease in blood hemoglobin levels and red blood cell counts.

5.6. OTHER RELEVANT INFORMATION

As reported in the English abstracts of several Russian studies (Moskalenko, 1966; Vasilenko, 1976; Vasilenko et al., 1972, 1974a), acute effects of oral exposure to the three isomers of nitroaniline include increased numbers of red blood cells, white blood cells (except for lymphocytes) and reticulocytes. Levels of methemoglobin in the blood were increased. Moskalenko (1966) indicated that hemoglobin levels were increased, but Vasilenko et al. (1972) indicated that hemoglobin levels were not affected by ingestion of o- or p-nitroaniline by rats. Heinz bodies and clumps of denatured hemoglobin (Walter and Israel, 1974), are a prominent feature of the red blood cells of animals exposed to or treated with the nitroanilines. Vasilenko et al. (1974a) indicated that oral administration of o-nitroaniline caused liver damage, although changes in liver weights were not reported to be an effect of p-nitroaniline exposure (10, 30 or 90 mg/m³) in rats (Nair et al., 1983). Oral administration of o- and p-nitroanline to

rats inhibited oxidative phosphorylation and decreased the ATP content of the liver (Kolodub and Vasilenko, 1976) and resulted in unspecified hepatotoxic effects (Vasilenko et al., 1974a,b).

An abstract describing the acute effects of poisoning in humans by the ingestion of the rodenticide Vacor reported that 5.1 mg of p-nitroaniline/kg of liver were identified in the victim's liver (Osteryoung et al., 1977). Acute exposure of humans to p-nitroaniline resulted in the onset of headache, cyanosis and dyspnea several hours after exposure (Anderson, 1946; Belknap, 1957). In humans p-nitroaniline absorption, whether from inhalation of the vapor or absorption of the solid through skin causes anoxia due to the formation of methemoglobin; jaundice and anemia have also been reported (OSHA/NIOSH, 1978). Short-term exposure causes mild irritation of the nose, throat and eyes and may cause some corneal damage (OSHA/NIOSH, 1978).

6. AQUATIC TOXICITY

6.1. ACUTE

Several investigators have studied the acute toxicity of p-nitroaniline in aquatic organisms. Curtis and Ward (1981) reported the 96 hour LC_{50} of p-nitroaniline to be 106.1 ppm in the fathead minnow, Pimephales promelas, whereas Wellens (1982) obtained a 96 hour LC_{50} of 87.6 ppm in the Zebra fish Brachydanio rerio. In the golden orfe, Leucisucs idus melanotus, the LC_{50} of p-nitroaniline was 35 ppm, the LC_{100} was 80 ppm, and the LC_{0} was 10 ppm (Juhnke and Luedemann, 1978). Tonogai et al. (1982) determined the 48-hour median threshold limit (TL_m) of p-nitroaniline to be 50 ppm in the himedaka fish Oryzias latipes. Exposure of rainbow trout to p-nitroaniline at 85 ppm for 48 hours produced 100% mortality, while 100% survival was obtained at 18.3 ppm. At 28-56 ppm, <100% mortality was observed (Lysak and Marcinek, 1972).

In the invertebrate, Daphnia magna, the LC_{50} of p-nitroaniline of 24 ppm was observed (Bringmann and Kuehn, 1977). In a later study (Bringmann and Kuehn, 1982), 2.5 ppm p-nitroaniline immobilized Daphnia magna with a median effective concentration (EC_{50}) of 2.5 ppm. The "toxic threshold" (concentration that decreases test populations by $\geq$5%) of p-nitroaniline was 6.9 ppm in the protozoan, Entosiphon sulcatum (Bringmann, 1978) and 3.1 ppm in the protozoan, Uronema parduczi (Bringmann and Kuehn, 1980a). No acute toxicity data were located for other nitroaniline isomers.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of the nitroaniline isomers to aquatic animals were not located in the literature as cited in the Appendix.

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978) established a p-nitroaniline toxic threshold (concentration that reduces population growth relative to controls after 8 days) of 0.35 ppm in the bluegreen alga, Microcystis aeruginosa, and 11 ppm in the green alga, Scenedesmus quadricauda. Bringmann and Kuehn (1980b) also obtained a toxic threshold of 4 ppm in the bacteria, Pseudomonas putida.

6.4. RESIDUE

Although no data were located on nitroaniline residue levels in aquatic organisms, Tonogai et al. (1982) reported an octanol/water partition coefficient of 3 for p-nitroaniline, which suggests little potential for bioaccumulation of residues.

7. EXISTING GUIDELINES

The ACGIH (1983) currently recommends a TLV of 3 mg/m^3 for an 8-hour TWA exposure to p-nitroaniline. No STEL is recommended, but the potential absorption of p-nitroaniline through the skin, mucous membranes, eyes and respiratory tract, is indicated (ACGIH, 1983). The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) has adopted an 8-hour TWA standard for occupational p-nitroaniline exposure of 6 mg/m^3 (1 ppm).

8. RISK ASSESSMENT

Although the National Toxicology Program (NTP, 1984) has completed its prechronic testing of p-nitroaniline administered to mice by gavage, no pertinent data regarding the carcinogenicity and/or chronic toxicity of any of the nitroanilines were located in the available literature. Pertinent data regarding the teratogenicity or reproductive effects of the nitroanilines also were not located in the available literature. Garner and Nutman (1977) reported that o-nitroaniline was mutagenic to S. typhimurium strain TA1538 in the presence of rat liver microsomal preparations. m-Nitroaniline was mutagenic to S. typhimurium strains TA98, TA100, TA1535 and TA1538 in the presence of the S-9 microsomal fraction (Thompson et al., 1983; Garner and Nutman, 1977), but not in its absence (Chiu et al., 1978). p-Nitroaniline was mutagenic to S. typhimurium strains TA98, TA1538 and D3052 in the presence of the S-9 microsomal fraction (Thompson et al., 1983; Garner and Nutman, 1977; Shah and Andrews, 1979; Haworth et al., 1983), as well as in its absence (Chiu et al., 1978; Haworth et al., 1983) and caused chromosome aberrations and sister chromatid exchanges in CHO cells in vitro (NTP, n.d.). The nitroaniline isomers did not damage DNA directly, as evidenced by the number of single-strand DNA-breaks in hepatic and renal cells (Cesarone et al., 1982) and the amount of unscheduled DNA synthesis in primary cultures of adult rat liver cells (Thompson et al., 1983). However, these tests were limited in dose range and, therefore, these results are not regarded as conclusive.

The results of a 90-day gavage study (Houser et al., 1983) indicated that there was a dose-related increase in methemoglobin, as well as a decrease in hematocrit and hemoglobin levels in rats, which was discernible

at the lowest level (3 mg/kg bw/day) of p-nitroaniline tested. The lowest level of p-nitroaniline tested also caused histopathological alterations in the spleen (Houser et al., 1983). Although the rat inhalation study reported by Nair et al. (1983) was only for a 4-week period, the effects produced by nitroaniline exposure on the spleen and blood were similar to those described in the Houser et al. (1983) gavage study. The lowest exposure from the Nair et al. (1983) study that elicited spleen effects (10 mg/m^3, 6 hours/day, 5 days/week) can be expressed as mg/kg/day by multiplying the concentration in air by the hours of exposure per day (6/24), the days of exposure per week (5/7), an assumed respiratory absorption rate (0.5) and an assumed inhalation rate [$0.105\ (0.35/0.113)^{2/3}$], and dividing by the assumed weight of a rat (0.35 kg). This calculation indicates that exposure to 10 mg/m^3 provided a dose of 0.57 mg/kg/day of p-nitroaniline. This calculation supports the results of the Houser et al. (1983) study and suggests that adverse effects from p-nitroaniline may occur at dose levels <3 mg/kg/day.

The data base for the toxicity of o-, m- and p-nitroaniline is insufficient for the derviation of an ADI. No chronic studies of these compounds were located in the available literature. In the only available subchronic study, p-nitropropane was administered orally to rats (Houser et al., 1983). The lowest dosage tested, 3 mg/kg bw/day, produced adverse effects. The severity of these effects could not be evaluated fully due to the lack of detail in the report, a meeting abstract. Results of a 4-week inhalation study in rats (Nair et al., 1983) indicate that adverse effects may occur at absorbed doses of p-nitroaniline <3 mg/kg/day.

9. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

There is only one subchronic study of sufficient detail and duration which could be used to derive a Reportable Quantity (RQ) ranking for p-nitroaniline. Unfortunately, the study is published only in abstract form (Houser et al., 1983). Because the results reported by the Houser et al. (1983) 90-day study are consistent with the results reported in shorter studies (Chhabra et al., 1983; Nair et al., 1983), in an English abstract of a Russian subchronic study (Vasilenko et al., 1974a), in studies of human poisonings (Anderson, 1946; Belknap, 1957) and in English abstracts of Russian studies on the acute effects of p-nitroaniline ingestion and/or inhalation (Moskalenko, 1966; Vasilenko, 1976; Vasilenko et al., 1972, 1974a,b), an RQ can be derived.

To derive the MED, the subchronic LOAEL (3 mg/kg bw/day) from the Houser et al. (1983) study is first divided by 10 to estimate a corresponding chronic value and subsequently multiplied by the cube root of the ratio of the rat animal body weight (0.35 kg, estimated) to human body weight (70 kg, estimated). Multiplying by 70 kg gives a human MED of 3.6 mg/day, which corresponds to an RV_d of 4.7. Because there were several changes in the physiological activity of the spleen (excessive extramedullary hemopoiesis, hemosiderosis, vacuolization of the red pulp and congestion), as well as decreased oxygen-carrying ability of the blood (increased blood levels of methemoglobin, decreased hematocrit and hemoglobin levels), an RV_e of 7 was assigned. The CS, which is the product of the RV_d and the RV_e, is 32.9, which corresponds to an RQ of 100 (Tables 9-1 and 9-2).

TABLE 9-1

Composite Score for the Toxicity of p-Nitroaniline[a]

Route	Species	Dose/Exposure	Human MED (mg/day)[b]	RV_d	Effects	RV_e	CS	RQ
Oral (gavage)	rats	3 mg/kg bw/day for 90 days	3.6	4.7	decreased oxygen-carrying ability of the blood; splenic histopathology	7	32.9	100

[a]Source: Houser et al., 1983

[b]An uncertainty factor of 10 was applied to convert from subchronic to chronic exposure.

TABLE 9-2

p-NITROANILINE

MINIMUM EFFECTIVE DOSE (MED) AND REPORTABLE QUANTITY (RQ)

Route:	oral
Dose*:	4.7 mg/day
Effect:	reduced oxygen-carrying capacity of blood, splenic histopathology
Reference:	Houser et al., 1983
RV_d:	4.7
RV_e:	7
Composite Score:	32.9
RQ:	100

*Equivalent Human Dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. 593 p.

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ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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In addition, the following document was reviewed to ensure that no key studies were overlooked in the preparation of this profile:

U.S. EPA. 1983. Draft Assessment of Testing Needs: Aniline and Chloro-, Bromo- and Nitroanilines. Support Document, Proposed Health and Environmental Effects Test Rule. Toxic Substances Control Act, Section 4. Office of Toxic Substances, U.S. EPA, Washington, DC, November, 1983.